

University of Groningen

Glycogen Storage Disease type IIIa

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DOI:
[10.33612/diss.130704555](https://doi.org/10.33612/diss.130704555)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Hoogeveen, I. (2020). *Glycogen Storage Disease type IIIa: towards precision medicine*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.130704555>

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A PRELIMINARY STUDY OF TELEMEDICINE FOR PATIENTS WITH HEPATIC GLYCOGEN STORAGE DISEASE AND THEIR HEALTHCARE PROVIDERS: FROM BEDSIDE TO HOME SITE MONITORING.

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Journal of Inherited Metabolic Disease 2018;41(6):929-936

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ABSTRACT

Background - The purpose of this project was to develop a telemedicine platform that supports home site monitoring and integrates biochemical, physiological and dietary parameters for individual patients with hepatic glycogen storage disease (GSD).

Methods and Results - The GSD Communication Platform (GCP) was designed with input from software developers, GSD patients, researchers and healthcare providers. In phase 1, prototyping and software design of the GCP has occurred. The GCP was composed of a GSD App for patients and a GSD Clinical Dashboard for healthcare providers. In phase 2, the GCP was tested by retrospective patient data entry. The following software functionalities were included (a) dietary registration and prescription module, (b) emergency protocol module and (c) data import functions for continuous glucose monitor devices and activity wearables. In phase 3, the GSD App was implemented in a pilot study of 8 patients with GSDIa (n=3), GSDIIIa (n=1) and GSDIX (n=4). Usability was measured by the system usability scale (SUS). The mean SUS score was 64/100 [range: 38-95].

Conclusions - This report describes the design, development and validation process of a telemedicine platform for patients with hepatic GSD. The GCP can facilitate home site monitoring and data exchange between patients with hepatic GSD and healthcare providers under varying circumstances. In the future, the GCP may support cross-border healthcare, second opinion processes and clinical trials, and could possibly also be adapted for other diseases for which a medical diet is the cornerstone.

SYNOPSIS

The authors of this study describe the design, development and validation process of a telemedicine platform for patients with hepatic glycogen storage disease to support home site monitoring and the integration of biochemical, physiological and dietary parameters.

INTRODUCTION

Hepatic glycogen storage diseases (GSDs) are a group of inborn errors of carbohydrate metabolism, for which a strict diet is the cornerstone of management. Patients with hepatic GSD display perturbed glucose homeostasis due to a deficiency of a functional enzyme or transporter in glycogen synthesis, glycogenolysis and/or gluconeogenesis. This generally leads to fasting intolerance, failure to thrive and hepatomegaly, and is biochemically associated with (non) ketotic hypoglycemia, (fasting or postprandial) hyperlactacidemia, increased liver enzymes and hyperlipidemia¹. The aim of dietary management is to maintain euglycemia, to suppress secondary metabolic derangements and to prevent long-term complications. The natural histories of several subtypes of hepatic GSD were reported by international cohort studies^{2,3}, review articles⁴⁻⁸, and guidelines⁹⁻¹².

In line with the observations that strict diabetes management prevents long-term complications, observational cohort studies in GSDI patients have emphasized the importance of good metabolic control for the prevention of liver adenomas¹³, nephropathy¹⁴⁻¹⁷ and bone disease^{18,19}. In GSDIIIa patients an association between overtreatment with carbohydrates and hypertrophic cardiomyopathy was suggested by several case-reports²⁰⁻²². In addition, a case report on two patients with GSDIXa presented improvement in liver cirrhosis on ultrasound after improving metabolic control²³.

Continuous glucose monitoring (CGM) systems have been developed to facilitate glucose monitoring. Originally, CGM systems were developed for patients with diabetes mellitus (DM)²⁴, but the application of CGM in GSD patients has also been reported by several groups²⁵⁻²⁸. The introduction of CGM systems has increased opportunities for home site monitoring. Nevertheless, day-to-day healthcare for the GSD patients is still challenging of which suboptimal metabolic control is only one of many reasons (as summarized in table 1).

Telemedicine (TM) has emerged rapidly as a novel tool to deliver healthcare tailored to the individual patient needs²⁹⁻³¹. Besides this, TM seems promising to provide cross-border healthcare for patients with rare diseases³². Surprisingly, to date, there is only one publication on a mobile application for dietary management of patients with inborn errors of metabolism³³.

To support home site monitoring and to integrate biochemical, physiological and dietary parameters, we have designed, validated and implemented a TM platform for patients with hepatic GSD. This TM platform, now further referred to as GSD Communication Platform (GCP), consists of the GSD Application (GSD App) for patients and their caregivers and the GSD Clinical Dashboard for healthcare providers.

1.	Suboptimal metabolic control (due to under- or overtreatment with carbohydrates) still occurs, associated with co-morbidity and long-term complications.
2.	There is a gap of knowledge between clinical guidelines and management in daily practice.
3.	There is large heterogeneity between individual patients with identical GSD subtypes and genotypes
4.	There is a discrepancy between prescribed diets and actual used diets.
5.	Clinical parameters are mostly measured in the hospital on relatively random moments.
6.	Traditional biomarkers are suboptimal and biochemically distant from the primary metabolic block.
7.	Patients with rare diseases usually do not live close to so-called centers of expertise, which challenges 'shared care models'.

Table 1 Challenges in current healthcare for individual patients with hepatic GSD.

METHODS

The GCP was intended to *support* rather than replace current healthcare as provided by our center of expertise for hepatic GSD and recommendations were only generated after approval by a healthcare provider. The usability pilot study has been carried out in accordance with ethical and legal guidelines of the University Medical Center Groningen (Medical Ethical Committee, 2016 / 466) and The Code of Ethics of the World Medical Association (Declaration of Helsinki). Technical documentation and user manuals of the GCP were prepared for the validation of the GCP as a class I medical device, as described in the Medical Device Directive 93/42/EEC. The creation of the technical documentation was supported by DRS consultancy and subsequently reviewed by the quality consultant medical devices of the University Medical Center Groningen, in preparation of notifying the GCP to the national Inspectorate of Health for a Conformité Européenne (CE) mark.

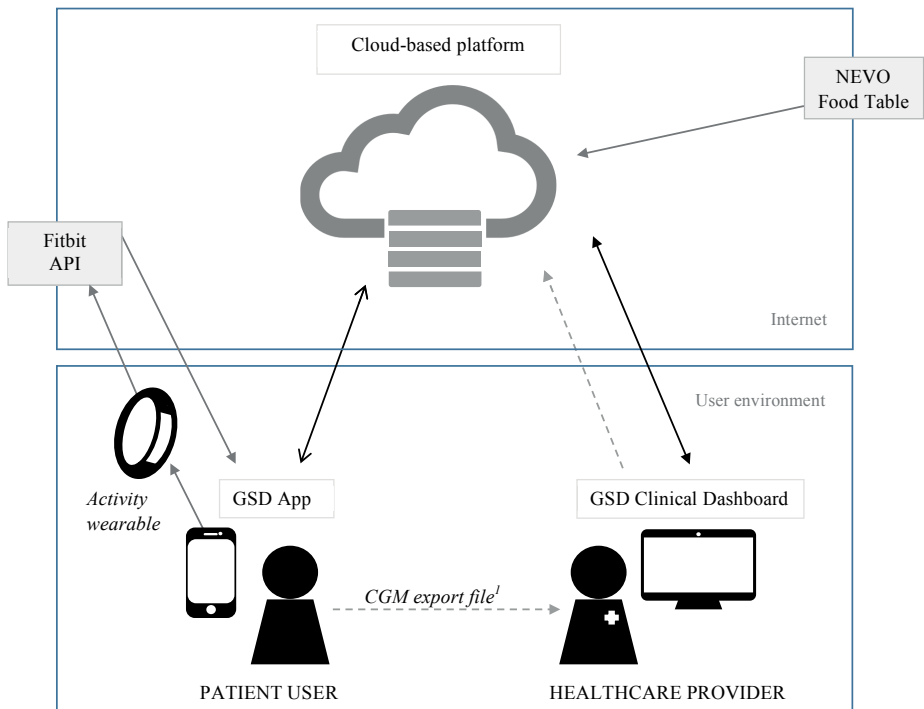
For the software development and validation process of the GCP, three phases were constructed.

Phase I – Prototyping and software design:

The GCP was designed during monthly meetings with input from software developers, (parents of) GSD patients, researchers and healthcare providers from June 2014 till present. The GCP was composed of two web applications; the GSD App for patients and their caregivers and the GSD Clinical Dashboard for healthcare providers. The GSD App was developed in Dutch, the native language for most of our patients, whereas the GSD Clinical Dashboard was developed in English. Figure 1 presents the detailed architecture of the GCP.

Intended uses - The intended use of the GSD App is to allow individuals with hepatic GSD to support their dietary management provided by healthcare providers, under normal circumstances and intercurrent illness, by monitoring and sharing home site collected data with healthcare providers. The intended use of the GSD Clinical Dashboard is to integrate data collected by hepatic GSD patients, either at home or during a hospital admission, and to provide subsequent GSD dietary management advises for normal circumstances, intercurrent illness and those situations where the emergency protocol is applicable.

Figure 1. Architecture of the GSD Communication Platform.



Legend: ¹, no API was available for the CGM data, these data were manually imported to the GSD Clinical Dashboard by the healthcare provider. API, application programming interface; CGM, continuous glucose monitoring; GSD, glycogen storage disease.

Data security and management – For both applications, the Hypertext Transfer Protocol Secure (HTTPS) and the Open Web Application Security Project Top Ten awareness document (<https://www.owasp.org/>) was adopted to secure integrity and privacy of online communication within the GCP. Access to the applications required a username and password. Passwords were stored with a salted and one-way encryption method to protect from accidental or unlawful loss. Software test plans and complaints management procedures were set up for post-market evaluation. The GCP was hosted on Microsoft Azure (refer to Azure subscription agreement: <https://azure.microsoft.com/en-us/support/legal/subscription-agreement/>). For the GSD App development, the open source frameworks AngularJS, JavaScript jQuery and Bootstrap were chosen. A non-commercial license from Highcharts (<https://www.highcharts.com>) was used to display the graphs in the GSD Clinical Dashboard.

Phase II – Software development and retrospective clinical data entry:

Features and functionality were reviewed and issues on usability were managed, processed and documented with the use of a Jira issue tracker from Atlassian® by software developers, researchers and healthcare providers.

The following software functionalities were included:

Dietary registration and prescription module - The Dutch Food Composition Table was used for the development of the dietary registration module in the GSD App and the prescription module for dieticians in the GSD Clinical Dashboard, respectively. The NEVO table contains information on macro- and micronutrients content and total kilocalories of all food items frequently eaten by the Dutch population. The NEVO table also includes data on the medical formulas, dietary supplements, maltodextrin products and uncooked cornstarch, such as Glycosade®.

Emergency protocol module – The local hospital emergency protocol guideline was used as a template for the emergency protocol module in the GSD Clinical Dashboard. The emergency protocol module was designed in such a way that it could automatically generate an emergency letter with the use of the patient's GSD type and actual body weight. After generation, the emergency letter was shared with the corresponding patient in the GSD App.

Data import functions – In the GSD Clinical Dashboard an import function for CGM data (Dexcom G4/G5 CGM system, Dexcom Inc., San Diego, CA) was created. An Application Programming Interface (API) was acquired by Fitbit, Inc. to import data from the activity wearable in the GSD App.

Retrospective data entry – Data from written food and clinical measurement diaries were retrospectively collected in the GCP by the researchers to test the usability and correctness of the GCP functionalities. These data were from patients who visited the University Medical Center Groningen GSD center of expertise between March and October 2016 and who gave written informed consent for the use of their data collected during their visit.

Phase III – Implementation and pilot study prospective clinical data entry:

Subjects and pilot study design – Between March and July 2017, data were prospectively collected in the GCP by selected GSD patients visiting our center. Patients were introduced to the GSD App by the treating physician (TGJD) and researcher (IJH). All subjects received an up-to-date manual for the use of the GSD App. Data exchange was requested by the healthcare provider to allow individual data integration in the GCP and critical follow-up after dietary changes. Subjects were asked to use the GSD App for home site monitoring before, during and/or after a clinic visit, according to the purpose of their visit. Furthermore, subjects could temporarily use an activity wearable with a heart rate function (Fitbit Charge HR™). A CGM system by Dexcom was used only when needed for regular care. Data from the CGM were retrospectively imported in the GSD Clinical Dashboard by the healthcare providers. Results of data integration in the GSD Clinical Dashboard (i.e. updated dietary plans and emergency protocols) were discussed with the subjects/patients

and their parents during the outpatient clinic visit and/or via a telephone or videoconference consultation following the (outpatient) clinic visit.

Survey methods – User feedback was documented in a structured logbook and usability issues from different users (patients, caregivers and healthcare providers) were uploaded in the Jira issue tracker for further software improvements. Subjects and/or caregivers were asked to give feedback on the GSD App via an open feedback form on paper or electronically via a SurveyMonkey questionnaire and to fill in the system usability scale (SUS)³⁴. An adjective scale was used for the interpretation of individual SUS scores³⁵.

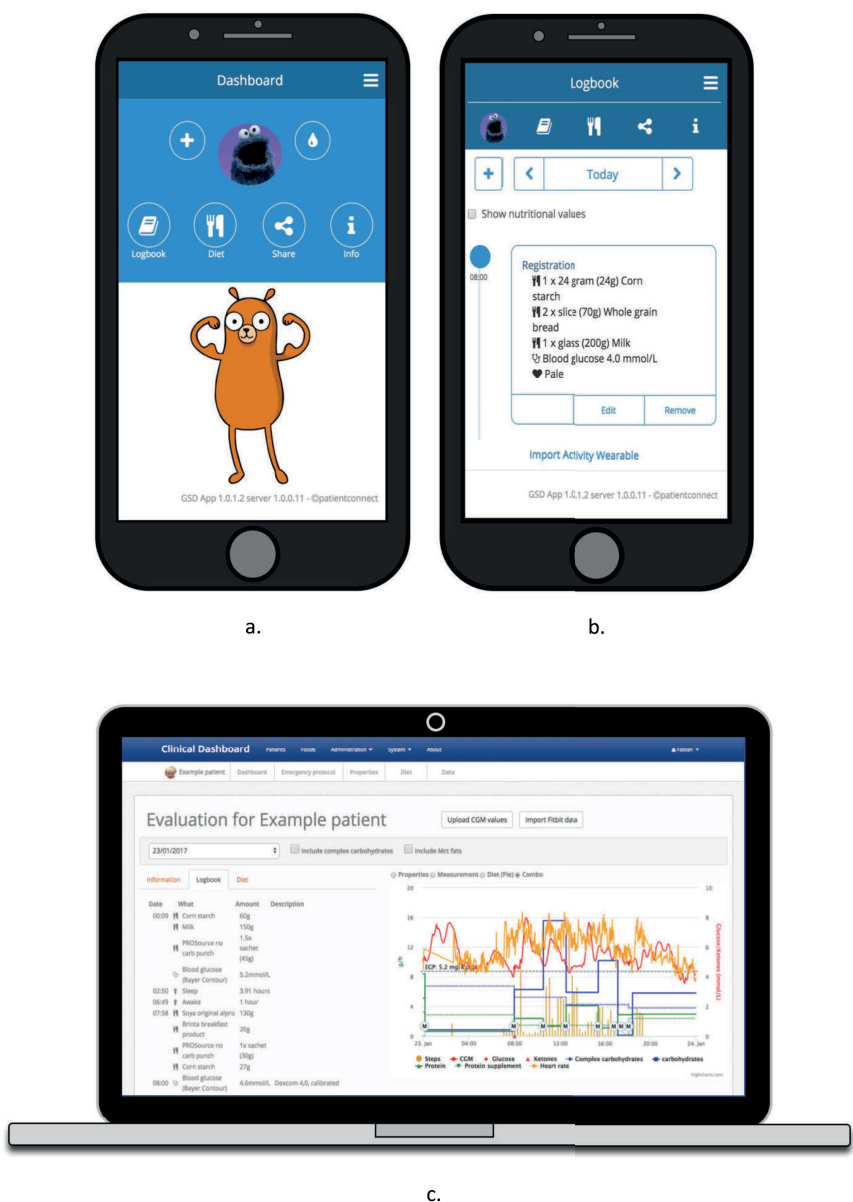
RESULTS

Phase I – Prototyping and software design:

Figure 2 displays screenshots of the GSD App and the GSD Clinical Dashboard. The GSD App can be accessed by going to <https://app.gsdapp.nl> in the internet browser on a mobile phone. The GSD Clinical Dashboard can be accessed via a desktop browser: <https://clinicaldashboard.gsdapp.nl>.

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Figure 2. Screenshots from the GSD App and the GSD Clinical Dashboard; a) the home screen, b) the logbook, c) evaluation display in the GSD Clinical Dashboard.



Legend: a) the cutlery button presents the prescribed diets; the share button displays the users and the shared data periods. The emergency protocol and personal emergency phone numbers are accessible via the information button. b) the logbook gives a clear overview of all registered meals over the day in a chronological manner. Macronutrients totals can be displayed per food item, per meal and/or per day. Besides dietary registration, the GSD App allows patients to enter their blood glucose/ketones measurements, physical activities and symptoms. c) the combo graph in the GSD Clinical Dashboard presents all individual data in one interactive graph. Data sets can be added or deleted from the graph.

Phase II – Software development and retrospective clinical data entry:

Access to individual patient registered data in the GSD App was restricted to the patient user and their caregivers. Data share requests by healthcare providers via the GSD Clinical Dashboard (for instance, for the preparation of an outpatient clinic visit) were only answered by and with the permission of (the caregivers of) the patient.

Data import and visualization – The combo graph in the GSD Clinical Dashboard displayed combined data of the patient from the requested period in one interactive graph (see figure 2c). The GSD Clinical Dashboard also displayed a histogram and a pie chart to provide more insight into the differences in macronutrient distributions and total calorie intake between prescribed and registered diets.

Dietary prescription module – The implementation of the NEVO table supported dietary registration, prescription and macronutrients calculations. An extra function was added for the entry of drip-feeding to simplify the determination of the rate of drip-feeding in milliliters per hour, and the macronutrient intake.

Retrospective data entry – Table 2 summarizes retrospective data on dietary management and CGM profiles from five patients with GSDIa (n=3), GSDIIIa (n=1) and GSDIX (n=1). Improvements for dietary registration in the GSD App and data visuals in the GSD Clinical Dashboard were implemented. Eventually, retrospective data entry led to the development of the GSD App and GSD Clinical Dashboard versions for the usability pilot study in phase III.

Phase III – Implementation and pilot study prospective clinical entry:

Subjects – The GSD App was prospectively used by 8 patients with GSDIa (n=3), IIIa (n=1), and IX (n=4). Table 2 presents an overview of the patients' characteristics. Three patients participated in both the retrospective clinical data entry and the pilot study. The GSD App was used by both GSD patients (n=3) and caregivers (n=5). Patient #P01 used the GSD App together with her parents as a first step towards autonomy.

Pilot study outcome – Table 2 displays the different purposes for which the GSD App was used. In phase III (P02, P04-P08), data were collected in the GSD App outside the hospital environment. The distance to our hospital ranged between 158 and 397 kilometers, emphasizing the potential in home site monitoring. Only one patient used the activity wearable (Fitbit Charge HR™) to monitor heart rate and activity as extra physiological marker for the assessment of his sport regimen.

Feedback from users – Feedback on the GSD App could be collected for 7/8 GSD App users (see table 2), unfortunately #P02 hasn't returned written feedback, despite reminders. The mean SUS score was 64/100 [range: 38-95]. Two subjects scored the GSD App usability with 'Excellent' on the adjective scale for interpretation of individual SUS scores. The mean SUS was higher among parents with younger children (n=3, mean SUS 83) compared to adult patients or parents with older children (≥ 12 years of age) (n=4, mean SUS 50). Patients reported in the open feedback form that it was easy to have their dietary prescription at hand and that the GSD App worked more efficiently compared to the paper food diaries. Points for improvements were the search strategy for the right food items and the feedback from healthcare providers on registered data.

Pt nr.	Age ^a	GSD type	Sex	Purpose	Logbook entry ^b	CGM import	Activity import ^c	Dietary advices
Phase II: Retrospective clinical data entry								
R01	12	Ia	F	Nocturnal Glycosade® versus CNGDF	✓	✓	✓	✓
R02	31	Ia	M	Regular outpatient clinic visit for metabolic monitoring	✓	✓	✓	✓
R03	36	IIla	F	Monitoring introduction of MCT	✓	✓	✓	✓
R04	0	IX	M	Metabolic monitoring during breastfeeding on demand	-	✓	-	-
R05	19	Ia	M	Metabolic monitoring	✓	✓	-	✓
Phase III: Pilot study prospective clinical data entry								
					SUS score (1-100)			
P01	13	Ia	F	^Nocturnal Glycosade® versus CNGDF	✓	✓	-	✓ 38
P02	0	IX	M	^Regular outpatient clinic visit for metabolic monitoring	✓	✓	-	✓ no response
P03	31	Ia	F	Introduction of Glycosade® as late night drink	✓	✓	-	✓ 55
P04	1	IX	M	Regular outpatient clinic visit for metabolic monitoring	✓	✓	-	✓ 93
P05	50	IX	M	Monitor of sport regimen	✓	-	✓	- 63
P06	4	IIla	F	Regular outpatient clinic visit for metabolic monitoring	✓	-	-	✓ 75
P07	20	Ia	M	^Regular outpatient clinic visit for metabolic monitoring	✓	✓	-	✓ 45
P08	5	IXc	M	Regular outpatient clinic visit for metabolic monitoring	✓	-	-	✓ 80

Table 2. Patient characteristics for phase II and III data collection in the GCP.

Legend: ^aAge of the patient during data period entered in the GSD App, ^bLogbook entry included dietary registration and measurements, ^cimport of activity wearable data by Fitbit, ^dthis patient was also included in the retrospective clinical data entry. CGM, continuous glucose monitoring; CNGDF, continuous nocturnal gastric drip feeding; MCT, medium chain triglycerides; SUS, system usability scale.

DISCUSSION

This report describes the design, development and validation process of a TM platform for patients with hepatic GSD. The GCP can facilitate home site monitoring and data exchange between patients with hepatic GSD and healthcare providers under varying circumstances. Rather than a study or a project, the development and maintenance of a TM platform for medical use is a continuous process responding to individual needs of patients and healthcare providers, technological and societal advancements, and the changing (international) legislation, as discussed below.

The GCP has been developed as a supportive tool for GSD patients and healthcare providers in our center of expertise. The GSD App allows patients to easily collect data at home as a preparation for an outpatient clinic visit, for the monitoring of in-hospital dietary interventions and for the evaluation of metabolic control at home and during physical activity. In addition, the GSD App gives patients access to their individual dietary management plan and emergency letter. Based on the collected SUS scores in the pilot study, it can be suggested that parents of GSD patients are in more need of a home site monitoring tool like the GSD App to manage everyday care for their child. The GSD Clinical Dashboard for healthcare providers facilitates diet prescription and emergency letter generation. Furthermore, the GSD Clinical Dashboard offers healthcare providers the possibility to analyze home site collected data from the individual patient. For several hepatic GSD subtypes there are international guidelines⁹⁻¹², but local and national circumstances need to be considered when the GCP would be implemented in other centers of expertise.

The connection of measure devices with the patient can be defined as the Internet of Things (IoT) in healthcare³⁶. IoT allows real-time and home site collected data sharing and integration, and eventually a better response to individual data. In general, data ownership within IoT is still in the gray area, because of the absence of transparent data regulation^{37,38}. We created different interactivities between the GCP and other technologies, such as the CGM systems and activity wearables. During the pilot study, data visuals within the GCP were only accessible for healthcare providers in the GSD Clinical Dashboard. An important point of feedback from the patients and their parents was the lack of interactivity of home site collected data and the visibility of these data in the GSD App for the patients themselves.

The revolution of internet has generated increasing interest for home site or remote monitoring in healthcare, that can overcome many of the issues as listed in table 1. The Dutch Federation of Medical Specialists published the vision document Medical Specialist 2025 that lists four essential requirements for future healthcare: (a) a holistic approach by the healthcare provider for each individual, unique patient, (b) digital developments to support network medicine, (c) focus on health, behavior and functional maintenance to prevent disease, and (d) implementation of big data analysis, wearables and home diagnostics in self-management of chronic diseases. More recently, Augustine and co-workers reported about a novel healthcare model for patients with rare diseases, that focusses on TM, integration of care and research; and improving patient–clinician–researcher

collaborations³⁹. In line with the so-called care continuum model, continuous maintenance and improvement of the GCP will occur in collaboration with the patients and their caregivers. Currently, there is only one report on a mobile application for dietary management of patients with inborn errors of metabolism³³. Our project may serve as an example to design, validate and implement a unique TM platform for and together with patients with rare diseases.

Some limitations need to be addressed. First, we performed a pilot study with a small number of patients only focusing on the usability and functionalities of the GSD App. Future research must focus on the effect of the GCP intervention on metabolic control, quality of life and cost-effectiveness. Usability of the GSD Clinical Dashboard for healthcare providers should also be studied. Second, new versions of the GSD App have been released in between the collection of SUS scores. Continuous improvement of the GSD App based on patient's feedback was possible due to close collaboration with the patient population and software developers, but therefore SUS score interpretation should be done with caution. Third, for the development of the GCP, the team collaborated especially with parents of GSD patients, hence the needs of (young) patients may have been underestimated.

Currently, the European Medical Device Directive 93/42/EEG is still the legal fundament guiding CE mark procedures of medical software, whereas ISO 14155:2011 addresses the good clinical practice of clinical investigations with humans to assess the safety and performance of medical devices. Since the start of our project, however, in our rapidly changing technological society, new European legislation has been approved regarding medical devices (i.e. the Medical Device Regulation MDR 2017/745) and data privacy (i.e. the General Data Protection Regulation). Hence, technical, societal, medical and legal developments are continuously influencing the process, demonstrating the complex dependency of different stakeholders to support healthcare for our patients and their caregivers.

Future perspectives and applications of the GCP are numerous. The platform could facilitate cross-border healthcare, support second opinion processes and provide support during clinical trials. In theory, the GCP could be adapted for patients with congenital hyperinsulinism and ketogenic diets (i.e. other rare conditions in which glucose homeostasis is perturbed) and inherited metabolic diseases for which a medical diet is the cornerstone. For these purposes, multiple translations and integration of the GCP with national food databases and electronic patient file systems will be crucial. The -in 2016 formally recognized- European Reference Network for Rare Hereditary Metabolic Disorders (MetabERN) could support the generation and (financial) maintenance of such TM projects^{40,41}, or alternatively, patient organizations.

FUNDING

This project was funded by Fonds NutsOhra (project 1402-028 to Terry G.J. Derks), the University Medical Center Groningen, Junior Scientific Masterclass (JSM MD/ PhD grants to Irene J. Hoogeveen and Fabian Peeks), and Round Table 34 Groningen.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs. Josca Westerhof (project manager at The Ubbo Emmius Fund, University of Groningen) for her help with the fundraising for this project. Mrs. Ellen Boelens-van der Knoop, Mr. Boelo Boelens and Mr. Janek Lueken are acknowledged for their support during the developmental phase of the application and the patients and their parents who have used the GSD App in the usability pilot study for their collaboration and useful feedback. We are thankful to Dr. Ilona Brouwer (biomedical engineer and quality consultant medical devices, University Medical Center Groningen) for critically reviewing the manuscript and the technical documentation.

REFERENCES

1. Walter J, Labrune P, Laforêt P. The Glycogen storage diseases and related disorders. In: Saudubray J-M, Baumgartner M, Walter J, eds. *Inborn Metabolic Diseases - Diagnosis and Treatment*. Berlin: Springer Berlin Heidelberg; 2016:121-137.
2. Rake J, Visser G, Labrune P, Leonard J, Ullrich K, Smit P. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr*. 2002;161:S20-S34.
3. Sentner CP, Hoogeveen IJ, Weinstein DA, et al. Glycogen storage disease type III: diagnosis, genotype, management, clinical course and outcome. *J Inherit Metab Dis*. 2016;39:697-704.
4. Dagli A, Sentner C, Weinstein D. Glycogen storage disease type III. In: Pagon R, Adam M, Ardinger H, eds. *GeneReviews [Internet]*. Seattle, University of Washington; 2016.
5. Goldstein JL, Austin SL, Kishnani PS. Phosphorylase Kinase Deficiency. In: Pagon R, Adam M, Ardinger H, eds. *GeneReviews [Internet]*. Seattle, University of Washington; 2011.
6. Dagli AI, Weinstein DA. Glycogen Storage Disease Type VI. In: Pagon R, Adam M, Ardinger H, eds. *GeneReviews [Internet]*. Seattle, University of Washington; 1993.
7. Magoulas PL E-HA. Glycogen storage disease type IV. In: Pagon RA, Adam MP AH, ed. *GeneReviews [Internet]*. University of Washington, Seattle; 2013.
8. Bali DS, Chen Y, Austin S GJ (2006). Glycogen storage disease type I. In: Pagon RA, AdamMP AH, ed. *GeneReviews [Internet]*. University of Washington, Seattle; 2006.
9. Rake JP, Visser G, Labrune P, Leonard J V, Ullrich K, Smit. Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr*. 2002;161:S112-S119.
10. Visser G, Rake J, Labrune P, et al. Consensus guidelines for management of glycogen storage disease type 1b - European Study on Glycogen Storage Disease Type 1. *Eur J Pediatr*. 2003;161:S120-S123.
11. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;128:1-29.
12. Kishnani PS, Austin SL, Arn P, et al. Glycogen Storage Disease Type III diagnosis and management guidelines. *Genet Med*. 2010;12:446-463.
13. Wang D, Fiske L, Carreras C, Weinstein D. Natural History of Hepatocellular Adenoma Formation in Glycogen Storage Disease type I. *J Pediatr*. 2011;159(3):442-446.
14. Melis D, Cozzolino M, Minopoli G, et al. Progression of renal damage in glycogen storage disease type I is associated to hyperlipidemia: a multicenter prospective Italian study. *J Pediatr*. 2015;166(4):1079-1082.
15. Okechuku GO, Shoemaker LR, Dambska M, Brown LM, Mathew J, Weinstein DA. Tight metabolic control plus ACE inhibitor therapy improves GSD I nephropathy. *J Inherit Metab Dis*. 2017;40(5):703-708.
16. Wolfsdorf JL, Laffel LMB, Crigler JF. Metabolic control and renal dysfunction in type I glycogen storage disease. *J Inherit Metab Dis*. 1997;20(4):559-568.
17. Martens DHJ, Rake JP, Navis G, Fidler V, Van Dael CML, Smit GPA. Renal function in glycogen storage disease type I, natural course, and renopreservative effects of ACE inhibition. *Clin J Am Soc Nephrol*. 2009;4(11):1741-1746.
18. Minarich LA, Kirpich A, Fiske LM, Weinstein DA. Bone mineral density in glycogen storage disease type Ia and Ib. *Genet Med*. 2012;14(8):737-741.
19. Melis D, Pivonello R, Cozzolino M, et al. Impaired bone metabolism in glycogen storage disease type 1 is associated with poor metabolic control in type 1a and with granulocyte colony-stimulating factor therapy in type 1b. *Horm Res Paediatr*. 2014;81(1):55-62.
20. Dagli AI, Zori RT, McCune H, Ivsc T, Maisenbacher M, Weinstein D. Reversal of glycogen storage disease type IIIa-related cardiomyopathy with modification of diet. *J Inherit Metab Dis*. 2009;32:S103-S106.
21. Valayannopoulos V, Bajolle F, Arnoux J, et al. Successful Treatment of Severe Cardiomyopathy in Glycogen Storage Disease Type III With D , L -3-Hydroxybutyrate , Ketogenic and High-Protein Diet. *Pediatr Res*. 2011;70(6):638-641.
22. Sentner CP, Caliskan K, Vletter WB, Smit GP (2012) Heart failure due to severe hypertrophic cardiomyopathy reversed by low calorie, high protein dietary adjustments in a glycogen storage disease type IIIa patient. *JIMD Rep*. 5:13–16
23. Tsilianidis LA, Fiske LM, Siegel S, et al. Aggressive therapy improves cirrhosis in glycogen storage disease type IX. *Mol Genet Metab*. 2013;109(2):179-182.

24. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW et al (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 359;1464-1476.
25. HersHKovitz E, Rachmel A, Ben-Zaken H, Phillip M. Continuous glucose monitoring in children with glycogen storage disease type I. *J Inherit Metab Dis*. 2001;24:863-869.
26. Maran A, Crepaldi C, Avogaro A, et al. Continuous glucose monitoring in conditions other than diabetes. *Diabetes Metab Res Rev*. 2004;20(Suppl 2):50-55.
27. White FJ, Jones SA. The use of continuous glucose monitoring in the practical management of glycogen storage disorders. *J Inherit Metab Dis*. 2011;34(3):631-642.
28. Kasapkara C, Cinasal Demir G, Hasanoglu A, Tümmer L. Continuous glucose monitoring in children with glycogen storage disease type I. *Eur J Clin Nutr*. 2014;68:101-105.
29. Moore M. Evolution of telemedicine. *Futur Gener Comput Syst*. 1999;15(2):245-254.
30. Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. *Sci Transl Med*. 2015;7(283):1-7.
31. Heintzman ND. A Digital Ecosystem of Diabetes Data and Technology: Services, Systems, and Tools Enabled by Wearables, Sensors, and Apps. *J Diabetes Sci Technol*. 2016;10(1):35-41.
32. Saliba V, Legido-Quigley H, Hallik R, Aaviksoo A, Car J, McKee M. Telemedicine across borders: A systematic review of factors that hinder or support implementation. *Int J Med Inform*. 2012;81(12):793-809.
33. Ho G, Ueda K, Houben RFA, et al. Metabolic Diet App Suite for inborn errors of amino acid metabolism. *Mol Genet Metab*. 2016;117(3):322-327.
34. Brooke J. SUS: a quick and dirty usability scale. In: Jordan PW, Thomas B, Weerdmeester BA M IL, ed. *Usability Evaluation in Industry*. London: Taylor and Francis; 1996:189-194.
35. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: Adding an adjective rating scale. *J usability Stud*. 2009;4(3):114-123.
36. Dimitrov D V. Medical internet of things and big data in healthcare. *Healthc Inform Res*. 2016;22(3):156-163.
37. Dinesen B, Nonnecke B, Lindeman D, et al. Personalized telehealth in the future: A global research agenda. *J Med Internet Res*. 2016;18(3).
38. Kostkova P, Brewer H, de Lusignan S, et al. Who Owns the Data? Open Data for Healthcare. *Front Public Heal*. 2016;4(February).
39. Augustine E, Dorsey E, Saltonstall P. The Care Continuum: An Evolving Model for Care and Research in Rare Diseases. *Pediatrics*. 2017;140(3).
40. Héon-Klin V. European Reference networks for rare diseases: What is the conceptual framework? *Orphanet J Rare Dis*. 2017;12(1):1-9.
41. Raposo VL. Telemedicine: The legal framework (or the lack of it) in Europe. *GMS Health Technol Assess*. 2016;12:1-12.

